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Clinical outcomes of topical epidermal growth factor in diabetic foot ulcers

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ABSTRACT

Aims: This study aims to evaluate the clinical outcomes of topical epidermal growth factor (EGF) in the treatment of diabetic foot ulcers (DFUs) in outpatient settings. It also seeks to provide guidance on the use of topical EGF, which is eligible for reimbursement for treating DFUs in our country.

Methods: A retrospective analysis involved 55 patients with DFUs who received topical EGF treatment. Patients received training on EGF application and were monitored for healing outcomes. Data were collected from medical records, including demographic information, wound characteristics, and laboratory results. Statistical analysis was performed using IBM SPSS version 25, employing chi-square, Pearson's correlation, and ANOVA tests to evaluate healing rates and associated factors.

Results: The study found that 70.9% of patients achieved complete wound closure within an average of 15.44 weeks. Healing rates were significantly higher for non-plantar wounds (83.8%) compared to plantar wounds (44.4%). Factors such as age, body weight, and body-mass index (BMI) were identified as influencing healing outcomes, with higher weights and BMI correlating with lower healing rates. Mild skin irritation was the only adverse effect reported.

Conclusion: Topical EGF demonstrates promising potential for enhancing the healing of DFUs in outpatient settings, achieving a healing rate comparable to specialized diabetic foot centers. The findings underscore the importance of considering patient-specific factors, such as obesity and adherence to treatment recommendations, to optimize healing outcomes. Further research with larger, multi-center studies is necessary to validate these results and improve access to effective treatments for patients with DFUs.

Keywords: Diabetic foot ulcers, epidermal growth factor, wound healing

INTRODUCTION

Diabetic foot ulcers (DFUs) are a common and severe complication of diabetes mellitus. The lifetime risk of foot ulcers is between 19% and 34%, and this figure is rising due to increased longevity and the medical complexity of individuals with diabetes.[1] These DFUs are a significant cause of morbidity, leading to prolonged hospital stays, increased healthcare costs, and, in severe cases, amputations. The pathogenesis of DFUs is multifactorial, involving peripheral neuropathy, peripheral vascular disease, and immune dysfunction. The chronic nature of these ulcers poses a challenge to effective management and healing.[2]

Growth factors are proteins that play a crucial role in the regulation of cellular processes, including proliferation, migration, and differentiation. They are essential for wound healing, as they promote the repair and regeneration of damaged tissues.[3] In the context of DFUs, growth factors can help overcome the impaired healing response associated with diabetes mellitus. Among these, epidermal growth factor (EGF) has garnered attention for its potential to enhance wound healing when applied topically.[4] EGF is a polypeptide that stimulates cell growth, proliferation, and differentiation by binding to its receptor, EGFR, on the cell surface. This interaction activates intracellular signaling pathways that promote epithelial cell migration and proliferation, essential processes in wound healing. EGF also enhances angiogenesis, the formation of new blood vessels, which is critical for supplying nutrients and oxygen to the healing tissue.[5] Topical EGF can be administered in various forms, including creams, gels, and sprays. The frequency of application varies, but it is

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typically applied once or twice daily to the wound bed after thorough cleaning.[6] Studies have suggested that debridement and infection control for ulcers should be performed before initiating EGF treatment.[7] Topical EGF is commonly used for wounds classified as Wagner stages 1 and 2.[7] For high-grade wounds, intralesional EGF can be utilized[8], although this treatment tends to be costly.[9] Prompt treatment of wounds in the early stages significantly reduces the risk of amputation, improves quality of life, and decreases healthcare costs for individuals with DFUs.[10]

This study aims to report the results of topical EGF gel application in outpatients with DFUs. The study also aims to offer guidance on the use of topical EGF, which is eligible for reimbursement for treating DFUs in our country.

METHODS

The study was conducted with the permission of Kayseri City Hospital Non-interventional Clinical Researches Ethics Committee (Date: 05.11.2024, Decision No: 237). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The retrospective evaluation includes patients admitted to our clinic between August 2022 and October 2024, who were followed as outpatients for one year period and received only wound cleansing and topical EGF application due to DFU. The medical records of 104 patients who met the inclusion criteria were reviewed. A data recording form was created with the ethics committee's approval. Data obtained through retrospective screening of the hospital automation system was recorded on this form, including age, gender, height, and body weight. Body-mass index (BMI), comorbidities, and past medications were also recorded. The patients' medical histories were recorded, including details such as the location of the wound, the grading of the wound, results from any cultures taken, hemogram values, blood levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), HbA1c value, and the duration of the wound healing process. The blood results obtained just before the start of treatment were evaluated. The wounds were categorized as plantar or non-plantar to assess the treatment's effect on different wound locations. Wagner staging, commonly used in studies involving topical EGF, was utilized to determine wound stages. Neuropathy data on the data record form were obtained during the first specialist examination when the diagnostic Semmes Weinstein monofilament and pinprick test were conducted. The initial specialist assessment identified several symptoms of poor circulation in the feet, including pale or cyanotic skin color, hair loss, and thinning of the skin. These observations were noted on the data record form as signs of circulatory disorders. Topical EGF was applied only to uninfected wounds. The treatment with topical EGF was started on infected and necrotic wounds after addressing the infection and surgically removing all dead tissue. This treatment started for grade 3 patients with abscesses or osteomyelitis after their infections were effectively treated through surgical or medical interventions. Patients who had previously undergone surgery were also noted. Patients were advised to avoid weight-bearing on the affected foot and to use double crutches for offloading. Patients aged 18 and older who were admitted to our clinic for DFUs and were prescribed topical EGF treatment, along with accessible patient information required for the study through the hospital automation system, were included in the study. Patients under 18 years old, those with incomplete information, those who used different wound care products during follow-up, and those who did not finish the follow-up were excluded from the study (**Figure 1**).

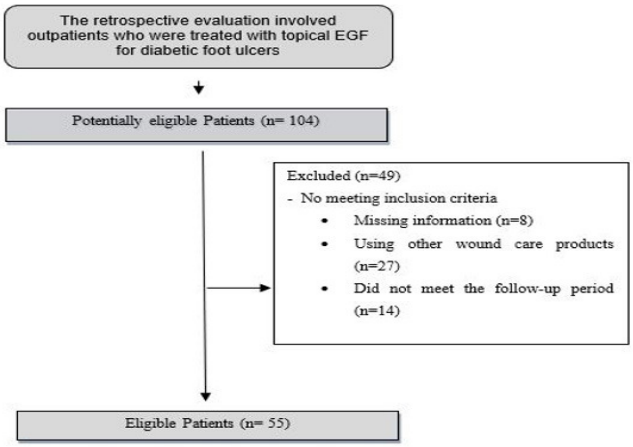
The retrospective evaluation involved outpatients who were treated with topical EGF for diabetic foot ulcers
Potentially eligible Patients (n= 104)
Excluded (n=49)
- No meeting inclusion criteria
• Missing information (n=8)
• Using other wound care products (n=27)
• Did not meet the follow-up period (n=14)
Eligible Patients (n= 55)

Figure 1. Study flow diagram

All patients received 10 minutes of theoretical training and 5 minutes of practical training on how to apply EGF to their wounds from the study director, a specialist physician on hyperbaric medicine, before participating in the study and starting treatment. The training included seeing each patient and their relative apply EGF to the wound site as the study director prescribes at least twice. After completing the training, all participating patients were prescribed topical EGF and instructed to apply a thin layer of the medication to their wounds twice a day, as recommended in the product's package insert. The dosage of the drug administered was 150 micrograms of recombinant EGF per gram. Complete closure of the wound was considered an indicator of successful healing. The criterion for failure was the absence of complete closure of the wound within one year. The study evaluates the rate and duration of wound healing while examining the correlation between wound healing and variables such as demographic data, laboratory results, and wound location.

Statistical Analysis

The data collected in the study were analyzed using the IBM SPSS version 25 statistical software package (SPSS Inc., Chicago, IL, USA). The normality of the data was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics were calculated using the Chi-square test. Pearson's correlation test was applied for normally distributed data, while Spearman's rho test was used for non-normally distributed data. $p<0.05$ was considered significant at a 95% confidence interval to determine statistical significance. The difference between independent groups was compared using the t-test. ANOVA test was used for data from more than two groups. The study evaluates the rate and duration of wound healing. Also, the correlation between wound healing and variables such as demographic data, laboratory results, and wound location is examined.

RESULTS

A total of 55 patients who were followed up for one year and met the inclusion criteria were included in the study. A total of two patients (3.63%) had wounds classified as Wagner stage 1, while 39 patients (70.9%) had stage 2 wounds, and 14 patients (25.5%) had deep, stage 3 wounds with healed infection. All patients exhibited varying degrees of peripheral neuropathy. The median age of the patients was 65 years, with a mean hemoglobin level of 12.5±1.8 g/dl. The median white blood cell count was 9.41, the CRP level was 13.0 mg/L, and the HbA1c level was 9.15 (Table 1). Complete wound closure was achieved in 39 patients (70.9%) within a mean of 15.44±8.35 weeks (Figure 2). However, the healing rate for non-plantar wounds was 83.8%, while the healing rate for plantar wounds was only 44.4%. The healing rate in patients with plantar lesions was significantly lower (p=0.003). Other factors that affected healing included age, weight, and BMI (Table 2).

Aside from mild skin irritation in two patients, no serious adverse events were reported during treatment, which did not necessitate treatment interruption.

Table 1. Demographic data, laboratory values, and examination results of the patients

Variable	Mean±SD	Median	Min-max
Height (cm)	170.88±8.41		155-188
Weight (kg)	79.41±13.11		60-110
Recovery time (week)	15.44±8.35		4-43
Wound duration (week)	25.06±28.32		2-144
Hb (g/dl)	12.5±1.8		9.6-17.7
BMI[a] (kg/m²)		27.20	21-43
Age (years)		65	37-82
WBC (10^3/μL)		9.41	5.07-16.93
CRP (mg/dl)		13.0	0.5-129
ESR (mm/h)		19.50	2-99
HbA1c (%)		9.15	6.1-13.9
	n	**%**	
Gender			
Male	40	72.7	
Female	15	27.3	
Plantar location of the lesion			
Yes	18	32.7	
No	37	67.3	
Signs of circulatory disorders			
No	16	29.1	
Yes	39	70.9	
Wagner phase			
1	2	3.6	
2	39	70.9	
3	14	25.5	
Treatment result			
Healed	39	70.9	
Not healed	16	29.1	
Operation			
No	47	85.5	
Yes	8	14.5	

Abbreviations: Hb: Haemoglobin, BMI: Body-mass index, WBC: White blood count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HbA1C: Haemoglobin A1C

DISCUSSION

Our study found that 70.9% of patients with DFUs treated as outpatients healed with only wound cleaning and a prescribed topical EGF gel. The healing rate is nearly identical to the one-year results from specialized diabetic foot centers.[11,12] It is not always feasible for patients with diabetic foot conditions to access diabetic foot centers. There are many barriers to access to diabetes foot care services for people with diabetes

Figure 2. Pre-treatment images (**a–d**) and post-treatment images (**e–h**) of patients with DFUs receiving a topical EGF jel

Table 2. Factors affecting recovery

Variable	Recovery+(n=39)	Recovery−(n=16)	p
Age (years)	65.41±9.50	58.00±10.74	0.013[β]
Gender			
Female	10	5	0.671[&]
Male	29	11	
Height (kg)	169.87±9.09	168.75±8.49	0.666[*]
Weight (cm)	78.41±12.81	88.38±11.30	**0.008**[*]
BMI (kg/m²)	26.98±3.55	31.03±5.66	**0.005**[β]
Plantar location of the lesion			**0.003**[&]
Yes	8	10	
No	31	6	
Signs of circulatory disorders			0.821[&]
Yes	28	11	
No	11	5	
Wagner phase			0.142[#]
1	2	0	
2	29	10	
3	8	6	
Hb (g/dl)	12.43±1.76	13.02±1.97	0.283[*]
WBC (10^3/μL)	9.91±2.78	11.03±5.76	0.853[β]
CRP (mg/dl)	23.85±33.37	23.56±27.32	0.753[β]
ESR (mm/h)	28.62±25.25	24.06±21.67	0.767[β]
HbA1c (%)	9.37±2.15	13.42±18.52	0.690[β]

*Independent sample T-test. & Phi correlation. # ANOVA test. β Mann-Whitney U Test. Hb: Haemoglobin, BMI: Body-mass index, WBC: White blood count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HbA1C: Haemoglobin A1C

mellitus.[13] Facilitating access to quality treatment is crucial for individuals at diabetic foot centers and those unable to access such facilities. Meta-analyses of clinical trials have provided robust evidence supporting the efficacy of EGF in DFUs.[14-16] Enhancing access to effective treatments like EGF is vital for improving healing outcomes for patients with DFUs, especially those unable to reach specialized diabetic foot centers.

Our study's findings show that participants who did not heal had significantly higher weight and BMI compared to those who achieved healing. There is currently no information in the literature regarding the relationship between the efficacy of topical EGF in DFUs and body weight. However, some studies have identified a negative correlation between serum EGF levels and BMI.[17,18] Furthermore, several obesity-related factors may lead to poor wound healing outcomes.[19] In obesity, fat cells grow larger without an increase in blood vessels, delaying angiogenesis. This leads to hypoxia due to insufficient oxygen, which can damage blood capillaries

and increase infection risk. Hypoxia also impairs essential collagen synthesis for wound healing. Additionally, vascular issues hinder immune cell recruitment and prolong inflammation. At the same time, nutritional deficiencies further complicate the healing process.[20] Additionally, wounds with a pathological inflammatory state and a high proteolytic microenvironment were considered to create an unfavorable environment for growth factors and their receptors.[21] Chronic low-grade inflammation in obesity may reduce treatment efficacy by affecting EGF and EGFR.[22,23] For these reasons, it may be posited that obesity was associated with non-recovery in our study.

Our study results showed that the age of those who recovered was significantly higher than that of those who did not recover. Two studies examined the relationship between the efficacy of topical topical EGF and age and found no significant difference.[24,25] However, it is known that the synthesis of growth factors declines with age. This reduction in EGF levels can slow the cell cycle and impair skin repair, negatively affecting the skin's ability to heal wounds effectively.[26] Therefore, using EGF in our study may provide a more targeted therapeutic strategy for treating wounds in elderly patients who are already deficient in endogenous growth factors.

In the present study, the location of the wounds was identified as plantar in 32.7% of the patients. The healing rate of plantar wounds was 44.4%, statistically significantly lower than that of non-plantar wounds. There is no information in the literature about the significant relationship between the efficacy of topical EGF and wound location in DFUs. An old study has demonstrated that topical growth factor is ineffective for plantar DFUs.[27] In a different study, topical growth factors significantly improved more than standard treatment in patients receiving a total contact cast for plantar DFUs.[28] In our study, patients were advised to refrain from weight-bearing on the affected foot. Patients often show poor adherence to these interventions, which affects their daily activities, partly due to the effectiveness of available offloading techniques.[29] In our study, patient non-compliance with offloading recommendations may have decreased the effectiveness of topical EGF for plantar wounds. Using topical EGF for plantar wounds without a total contact cast or effective offloading may not achieve the desired healing results.

Topical EGF is typically used for Wagner grade 1 and grade 2 wounds.[7,30] In our study, a significant proportion of participants (25.5%) had a non-infected grade 3 wound, unlike other studies. This study is the first to investigate the use of topical EGF in Wagner grade 3 wounds, and we found no significant differences in the results based on wound grade. Our findings suggest that topical EGF can also effectively treat non-infected deep ulcers.

Physicians treating DFUs often encounter considerable challenges, such as healing difficulties, complex management, and high costs. Administering this EGF gel to patients with clean, uninfected DFUs may provide an effective strategy for overcoming these challenges. In recent years, there has been a growing emphasis on involving the patient as a member of the care team and encouraging self-care for this complex condition.[31,32] Improved outcomes can be achieved by teaching appropriate outpatients how to apply topical EGF through a short training session, as it is easy to apply. A comparative analysis of patients treated as outpatients in a non-specialist setting and those treated at a diabetic foot center showed no significant differences in outcomes for patients with Wagner grades 2 and 3. However, the diabetic foot center demonstrated a higher improvement rate for patients with Wagner grade 4.[33] Effective treatment of DFUs relies on strong collaboration between patients and healthcare providers, with interventions tailored to individual needs across primary care and specialist settings.[34] The results of our study offer a solution for the follow-up care of clean grade 2 and grade 3 DFUs in outpatient settings at both primary care and diabetic foot centers. Given the challenges many patients encounter when accessing diabetic foot centers, it is essential for other outpatient clinics serving wound patients to adopt effective strategies that enable patients to engage in their treatment without facing financial burdens.[35]

Limitations

The study's retrospective nature limits causal inferences, as historical data may lead to biases in participant selection and recording of results, and caution is required in interpreting results. Furthermore, factors that may influence healing, such as the measurement of the wound's width and depth, could not be assessed due to the retrospective nature of this study. The fact that the study was conducted in a single center limits the generalisability of the findings, as differences in treatment protocols and patient demographic characteristics in different institutions may affect the results. The sample size may need further expansion to assess the success of this method reliably and in a generalizable manner.

CONCLUSION

Topical EGF shows promising potential for enhancing the healing of DFUs in outpatient settings, achieving a 70.9% healing rate similar to specialized diabetic foot centers. Healing success was influenced by body weight, BMI, and wound location, with higher body weights and plantar wounds leading to lower healing rates. These findings highlight the need to consider patient-specific factors, like obesity and adherence to treatment recommendations, to optimize outcomes. Further research with larger, multi-center studies is necessary to validate these results. Incorporating topical EGF into standard care for DFUs could improve access to effective treatment, especially for patients facing challenges in obtaining specialized care. By educating patients and encouraging self-care, healthcare providers can enhance healing outcomes and improve the quality of life for individuals with diabetes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Kayseri City Hospital Non-interventional Clinical Researches Ethics Committee (Date: 05.11.2024, Decision No: 237).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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